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Original article

High frequency of asymptomatic hyperparathyroidism in patients with fibromyalgia: random association or misdiagnosis?

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ABSTRACT

Fibromyalgia (FM) and hyperparathyroidism may present similar symptoms (musculoskeletal pain, cognitive disorders, insomnia, depression and anxiety), causing diagnostic confusion.

Objectives: To determine the frequency of asymptomatic hyperparathyroidism in a sample of patients with FM and to evaluate the association of laboratory abnormalities to clinical symptoms.

Methods: Cross-sectional study with 100 women with FM and 57 healthy women (comparison group). Parathyroid hormone (PTH), calcium and albumin levels were accessed, as well as symptoms in the FM group.

Results: In FM group, mean serum calcium (9.6 ± 0.98 mg/dL) and PTH (57.06 ± 68.98 pg/mL) values were considered normal, although PTH levels had been significantly higher than in the comparison group (37.12 ± 19.02 pg/mL; $p = 0.001$). Hypercalcemic hyperparathyroidism was diagnosed in 6% of patients with FM, and 17% of these women exhibited only high levels of PTH, featuring a normocalcemic hyperparathyroidism, with higher frequencies than those expected for their age. There was no significant association between hyperparathyroidism and FM symptoms, except for epigastric pain, which was more frequent in the group of patients concomitantly with both diseases ($p = 0.012$).

Conclusions: A high frequency of hyperparathyroidism was noted in women with FM *versus* the general population. Normocalcemic hyperparathyroidism was also more frequent in patients with FM. Longitudinal studies with greater number of patients are needed to assess whether this is an association by chance only, if the increased serum levels of PTH are part of FM pathophysiology, or even if these would not be cases of FM, but of hyperparathyroidism.

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Frequência elevada de hiperparatireoidismo assintomático em pacientes com fibromialgia: associação ao acaso ou erro diagnóstico?

Palavras-chave:
Fibromialgia
Hiperparatireoidismo
Dor musculoesquelética
Hipercalcemia

RESUMO

A fibromialgia (FM) e o hiperparatireoidismo podem apresentar sintomas semelhantes (dores osteomusculares, distúrbios cognitivos, insônia, depressão e ansiedade) e causar confusão diagnóstica.

Objetivos: Determinar a frequência de hiperparatireoidismo assintomático em uma amostra de pacientes com FM e avaliar a associação das alterações laboratoriais com a sintomatologia.

Metodologia: Estudo transversal com 100 mulheres portadoras de FM e 57 mulheres saudáveis (grupo de comparação). Foram pesquisados os níveis de paratormônio (PTH), cálcio e albumina, além da pesquisa de sintomas no grupo com FM.

Resultados: No grupo com FM, os valores médios de cálcio sérico (9,6 ± 0,98 mg/dL) e de PTH (57,06 ± 68,98pg/mL) foram considerados normais, embora os níveis de PTH tivessem sido significativamente maiores do que no grupo de comparação (37,12 ± 19,02 pg/mL; p = 0,001). O hiperparatireoidismo hipercalcêmico foi diagnosticado em 6% das pacientes com FM e 17% delas apresentaram apenas PTH elevado, o que caracterizou o hiperparatireoidismo normocalcêmico, frequências maiores do que esperada para a faixa etária. Não houve associação significativa entre hiperparatireoidismo e sintomas da FM, com exceção da epigastralgia, que foi mais frequente no grupo de pacientes com as duas doenças concomitantes (p = 0,012).

Conclusões: Houve frequência elevada de hiperparatireoidismo em portadoras de FM quanto à população geral. Hiperparatireoidismo normocalcêmico também foi mais frequente em pacientes com FM. Estudos longitudinais e com maior número de pacientes são necessários para avaliar se trata-se apenas de uma associação ao acaso, se as elevações séricas do PTH fazem parte da fisiopatologia da FM ou, ainda, se não seriam casos de FM, e sim de hiperparatireoidismo.

Introduction

Primary hyperparathyroidism (PHP), a disease caused by a hyperactive parathyroid and consequent hypercalcemia, is associated in 85–90% of cases, to the presence of solitary gland adenomas, occurring most commonly in people aged over 50 and in women in post-menopause, with a prevalence of 0.78% for the general population. Although the clinical presentation is variable, the asymptomatic hypercalcemia form is the most common (50–80%).[1,2]

Fibromyalgia (FM) is one of the most common rheumatic disorders, affecting approximately 2–8% of the population, depending on the diagnostic criteria used for its classification.[3] FM affects specially young women (30–55 years old),[4] but with the use of new classification criteria,[5] the prevalence in men has increased.[6] Its main feature is a diffuse and chronic musculoskeletal pain associated with symptoms such as fatigue, sleep disturbances, morning stiffness, diffuse paresthesias, a subjective feeling of edema, cognitive disorders, depression and anxiety.[7] The cause of FM is unknown, but its development is associated with a disorder of central nervous system regulation with respect to pain. So far, no significant laboratory abnormalities were identified in FM patients.[8]

Fatigue, arthralgia, myalgia, sleep disturbances, depression, anxiety and memory impairment – common symptoms in patients with FM – are part of the nonspecific symptoms in patients with PHP. Asymptomatic PHP is understood as that case in which laboratory changes are occurring, with elevated serum levels of parathyroid hormone (PTH) and calcium, without the presence of the classic manifestations of PHP, for instance, severe hypercalcemia, cystic fibrous osteitis and advanced kidney disease.[2] Starting in the 70s, with the acquisition of new knowledge and with improved techniques for the determination of calcium and PTH, it was observed that PHP is a common disorder, and usually has no serious or specific symptoms.[2] In a series of 124 cases of PHP evaluated in the city of Recife (Brazil), 47% had no symptoms related to the disease, while 25% suffered from cystic fibrous osteitis, 25% exhibited kidney stones without bone involvement, and 2% presented with typical neuropsychiatric syndrome.[9]

Another study involving 4207 patients aged over 18 in public and private endocrinology centers in Recife (Brazil), found a prevalence of 0.78% (95% CI, 0.52 to 1.04) of PHP, of which 81.8% were asymptomatic.[10] The ratio between women:men was 7.2:1, the mean age was 61 ± 16 years and 89.7% of affected females were postmenopausal. Among the typical manifestations of PHP, fibrous osteitis was present in 6.1% of cases, nephrolithiasis in 18.2%, and acute neuropsychiatric syndrome in 3%. The prevalence of nonspecific symptoms was 51.5% for fatigue and 39.3% for muscle weakness.[10]

A former study also conducted in Recife (Brazil) determined a prevalence of 1.3% of PHP in postmenopausal women. Of

this total, 50% of the cases presented in a form considered as asymptomatic, characterized by nonspecific symptoms such as fatigue, arthralgia, myalgia and sleep disorders.[11]

In patients with asymptomatic PHP, a rise in serum levels of calcium is found, but usually only 1 mg/dL above the upper limit of normal. In general, PTH levels are 1.5–2.0 times greater than the upper limit of normal, while the 24-hour urinary calcium tends to remain unchanged.[12]

Similar to FM, hyperparathyroidism also predominates in women, but in a little older age group (post-menopausal females), increasing in prevalence with age.[13,14] Despite the similarity between symptoms of FM and asymptomatic hyperparathyroidism, there are few publications evaluating this association. This study aimed to determine the frequency of asymptomatic hyperparathyroidism in women with FM, verify the association with clinical parameters, and compare the results of PTH and calcium found in healthy women.

Methodology

Patients

A cross-sectional, descriptive study was conducted between August 2011 and January 2012, and a total of 100 subjects from the Fibromyalgia Outpatient Clinic of the Rheumatology Department of the Hospital das Clinicas, Universidade Federal de Pernambuco (HC-UFPE) were included. For admission to the study, the participants should be 20–55-year old women and meet the criteria for classification and diagnosis of FM (FM Group) according to the American College of Rheumatology (ACR), respectively from 1990 and 2010.[5,15] Patients who refused to sign the consent form and those with a previous diagnosis of malignancy, bone metastases, granulomatous and/or infectious diseases, kidney disease, hyperthyroidism, hypothyroidism, and acromegaly, in addition to patients who were taking thiazide diuretics, lithium salts or in replacement therapy with calcium and vitamin D were excluded. Patients older than 55 years were also excluded to avoid a selection bias, since PHP is more common in this age group.

Apart from this group, samples of 57 healthy women were also collected, which formed the comparison group. Matched for age, the criteria for inclusion and exclusion of this group were the same to the study group, except for the diagnosis of FM.

Clinical and laboratory evaluation

The data collection protocol was always applied by the same researcher during an outpatient consultation; and information necessary for the study was acquired directly with the patient and supplemented by a review of her medical record. At the end of the consultation, blood was collected for serum calcium, albumin and PTH (intact molecule) determination. The amount of serum calcium was obtained using an autoanalyzer (ARCHITECT c Systems, Abbott, USA) whose adopted reference values range from 8.6 to 10.3 mg/dL with a 0.4 mg/dL detection limit. For the dosage of PTH a chemoilluminometric assay (IMMULITE 2000 DPC, Los Angeles, USA) was used, with reference values of 12–69 pg/mL and analytical sensitivity (lower detection limit which can be distinguished from zero) of 3.0 pg/mL. To serum albumin dosage, bromocresol dye, which specifically binds to albumin forming a colored complex, was used. The reference values vary from 3.2 to 5.2 g/dL, with a detection limit of 0.3 g/dL (ARCHITECT c Systems, Abbott, USA). In the presence of hypoalbuminemia (values <3.2 g/dL), serum calcium was corrected by following formula[16]:

$$\text{Corrected calcium (mg/dL)} = \text{Total calcium (mg/dL)} + 0.8 \times [4 - \text{albumin (g/dL)}]$$

All samples were processed in the HC-UFPE Laboratory. The study was approved by the Human Research Ethics Committee in the Health Sciences Center of UFPE and all study subjects signed an informed consent prior to having their data and blood samples collected.

Definition of variables

The variables evaluated in the study were defined as follows:

- *Depression*: a subjective feeling of sadness diagnosed by a psychiatrist or treatment with specific medications
- *Fatigue:* easy tiredness, lethargy without clinical signs to justify another specific disease
- *Myalgia:* muscle pain anywhere in the body
- *Arthralgia:* non-inflammatory, painful joint symptoms
- *Emotional lability:* depressive symptoms, anxiety, apprehension, irritability or nervousness
- *Headache:* any pain that occurs in one or more skull areas
- *Non-restorative sleep:* feeling tired upon waking
- *Changes in memory*: forgetting situations, difficulty concentrating on activities
- *Hyperparathyroidism:* hypercalcemia (calcium >10.3 mg/dL) and elevated PTH values (PTH >69 pg/mL)
- *Normocalcemic hyperparathyroidism:* high PTH (PTH >69 pg/mL) with normal levels of serum calcium.

Statistics

All tests were applied with a 95% confidence interval. The numeric variables are represented by measures of central tendency and dispersion measures. The Kolmogorov–Smirnov normality test for quantitative variables was used. To verify the existence of an association, Fisher's exact test for categorical variables and for comparison of two groups (Student *t* [normal distribution] and Mann–Whitney [non-normal distribution] test) was used. For statistical calculations, the software SPSS (*Statistical Package for Social Sciences*), version 17, was used.

Results

Among the total of 157 women who had their data collected, 100 were diagnosed with fibromyalgia and 57 were healthy. The mean (± SD) age of the patients with FM was 42.4 (± 8.42) years. As can be seen in Table 1, the mean values of calcium and PTH in patients with FM were within normal limits; however, PTH levels in the FM group were significantly higher *versus* comparison group ($p = 0.001$).

Table 1 – Distribution of means for age, serum calcium and parathyroid hormone in fibromyalgia and comparison groups.

Variables	Groups		p-Value
	FM Mean ± SD	Comparison Mean ± SD	
Age (years)	42.4 ± 8.42	41.3 ± 9.4	0.443[a]
Calcium (mg/dL)	9.6 ± 1.0	9.5 ± 0.3	0.612[b]
PTH (pg/mL)	57.1 ± 69.0	37.1 ± 19.0	0.001[b]

FM, fibromyalgia; SD, standard deviation; PTH, parathyroid hormone.
[a] Student's t test.
[b] Mann–Whitney test.

According to the criteria for defining hypercalcemic hyperparathyroidism, it was possible to diagnose the disease in six patients (6% frequency) with FM. No woman in comparison group had a diagnosis of PHP; but this difference was not statistically significant ($p = 0.087$). However, the frequency of normocalcemic hyperparathyroidism in FM patients was 17% in the FM group *versus* 5.2% in comparison group, with statistical significance ($p = 0.045$) (Table 2).

The prevalence of the most common symptoms of these two conditions was similar in FM women with and without hyperparathyroidism (Table 3). Except for epigastric pain ($p = 0.012$), no other symptoms were significantly associated with the presence of hyperparathyroidism.

Discussion

In our study, we observed a higher frequency of asymptomatic normocalcemic and hypercalcemic hyperparathyroidism (although not statistically significant for the latest manifestation) in patients with fibromyalgia, when compared to the group of healthy women. The frequency of 6% of hyperparathyroidism found in our sample of patients with FM is also higher than that expected for this age-matched population, as well as for the older population. In the general population, the prevalence of hyperparathyroidism for all ages is 0.3–0.5%.[17,18] A study in the city of Recife, Brazil showed a prevalence of 0.78%, and the vast majority (81.8%) were postmenopausal women.[10] Although we have not conducted a prevalence study with a large number of patients, our data indicate a higher frequency of hyperparathyroidism in patients with FM.

Table 2 – Frequency of hyperparathyroidism and normocalcemic hyperparathyroidism in fibromyalgia and comparison groups.

	Group		p-Value[a]
	FM ($n = 100$) n (%)	Comparison ($n = 57$) n (%)	
Hypercalcemic HP	6 (6.0)	0 (0.0)	0.087
Normocalcemic HP	17 (17.0)	3 (5.2)	0.045

HP, hyperparathyroidism; FM, fibromyalgia.
[a] Fisher's exact test.

Table 3 – Frequency of clinical symptoms of patients in fibromyalgia group, with and without hyperparathyroidism.

Variables	FM group		p-Value[a]
	With HP n (%)	Without HP n (%)	
Arthralgia	6 (100)	85 (90.4)	1.000
Myalgia	6 (100)	86 (91.5)	1.000
Headache	6 (100)	80 (85.1)	0.591
Depression	2 (33.3)	35 (37.2)	1.000
Fatigue	5 (83.3)	82 (87.2)	0.576
Non-restorative sleep	6 (100)	84 (89.4)	1.000
Memory change	5 (83.3)	66 (70.2)	0.669
Nausea/vomiting	3 (50)	44 (46.8)	1.000
Epigastric pain	6 (100)	43 (45.5)	0.012
Constipation	0 (0)	16 (17)	0.586
TMA pain	1 (16.7)	21 (22.3)	1.000
Urinary changes	0 (0)	16 (17)	0.586

FM, fibromyalgia; HP, hyperparathyroidism; TMA, temporomandibular joint.
[a] Fisher's exact test.

Another phenotype of hyperparathyroidism has been described, consisting of patients with normal serum calcium and with PTH elevation in the absence of other known cause for this hormonal increase: the normocalcemic hyperparathyroidism. It has been proposed that this entity would be the first phase of a biphasic disease, that later would become a case of hyperparathyroidism.[19] There are few population-based studies and the prevalence of normocalcemic hyperparathyroidism is not well established, although it may be between 0.4 and 3.1%. Normocalcemic hyperparathyroidism should be considered as part of the diagnostic spectrum of hyperparathyroidism, and such patients should be monitored with periodic laboratory determinations, with the aim of an early detection of hypercalcemia.[19] In our sample, the frequency of normocalcemic hyperparathyroidism was even higher (17%) than that for hypercalcemic hyperparathyroidism (6%), with a statistical difference in relation to the presence of this condition, when these findings were compared with those of healthy women. However, it would be necessary to obtain serum levels of vitamin D to assess its effect on calcium levels, which was not possible for this study, and this is its main limitation.

Currently, asymptomatic hypercalcemia is considered the most common form of presentation of PHP.[20] However, some studies have shown that, in fact, these patients exhibit symptoms, but because of its insidious and non-specific nature, these are not initially assigned specifically to PHP.[12,21] In a sample of 229 patients with PHP and with surgical indication, seen during a 15-month period, the most frequent symptoms were fatigue, asthenia, arthralgia, impaired concentration and memory, anxiety and depression.[22] In view of this context, the clinical presentation of PHP becomes similar to the picture presented by patients with FM,[23] requiring the

completion of laboratory tests to distinguish these two clinical entities.

Although these specific symptoms are quite frequent in patients with hyperparathyroidism, its etiology and relationship to specific laboratory abnormalities are still unknown. Although there is an improvement in symptoms after completion of parathyroidectomy,[24] it is unclear whether these symptoms are mediated by hypercalcemia, the elevation of PTH, or by some other unknown mechanism.[22] The correlation between the normalization of laboratory findings and the resolution of a large number of symptoms after the parathyroidectomy suggests that the symptoms associated with hyperparathyroidism are mediated by laboratory biochemical abnormalities.[22] Bargren et al. assessed if the severity of symptoms is related to serum calcium and PTH levels. It was unexpectedly observed that the majority of patients with bone or joint pain, depression, constipation and renal calculi had serum calcium levels <11.2 mg/dL, and there was no association of symptoms with PTH levels.[22] In our study, a relationship between PTH or calcium levels with the symptoms was also not found.

Vitamin D deficiency can occur in patients with FM,[25] but the results found in the literature are conflicting.[26–28] Currently, it is not known whether low serum levels of vitamin D could be part of the pathophysiology of the generation and maintenance of chronic pain, or a consequence of less mobility or of depressive symptoms leading to a lower sun exposure, or also of high rates of adiposity that decrease vitamin D synthesis.[29] A study published in 2010 and carried out in order to evaluate serum levels of vitamin D in patients with FM *versus* healthy controls, noted that there was no difference between the two groups, but the levels of PTH were significantly higher in patients with FM (59.9 ± 17.6 pg/L) than in the comparison group (48.5 ± 17.4 pg/L) ($p = 0.014$); in this study a relation between PTH levels and clinical symptoms was not evaluated.[30]

An interesting study in 2014 evaluated the presence of FM in hemodialysis patients, finding a frequency of 12.2%. Among patients with and without FM, there was no difference between epidemiological or clinical parameters related to dialysis. Also, there was no significant difference in laboratory parameters between the groups, except for PTH levels, which were higher in patients with FM ($p = 0.002$).[31]

Ferrari and Russell determined the prevalence of PHP in a sample of patients with FM, in patients with diffuse pain who did not meet criteria for FM, and in a group of patients with localized musculoskeletal pain. A prevalence of about 6% of PHP was found in these three groups – a result similar to ours, and which represents an index higher than that observed in the general population. The result of this study suggests the possibility of an association between PHP and diffuse or localized musculoskeletal pain.[32]

Several authors cite hyperparathyroidism as a differential diagnosis of musculoskeletal diseases, and there are reports in the literature of cases of PHP mistakenly diagnosed as FM.[33–35] In addition, among patients with symptoms of FM and PHP who underwent parathyroidectomy, 89% had improvement of symptoms of FM, and 77% and 21% decreased or discontinued, respectively, medications used for this purpose.[34]

In our study, none of the clinical symptoms similar to the two diseases, such as arthralgia, myalgia, non-restorative sleep, memory changes and depression was different between patients with FM with and without hyperparathyroidism, except in the case of epigastric pain, which was significantly more frequent in patients with increased PTH and calcium. Gastrointestinal manifestations of hyperparathyroidism are recognized for several decades, and may even be the initial isolated symptom.[36,37] Among the most common symptoms one can observe constipation (33%), epigastric pain (30%), nausea (24%) and loss of appetite (15%), with a significant reduction of these symptoms after parathyroidectomy.[38] The exact pathophysiological mechanism of these changes is not fully understood, but it is believed that atony of the gastrointestinal tract occurs as a result of the sustained stimulation of the PTH receptor, which would lead to constipation in the colon and to dyspepsia in the stomach.[39] Thus, perhaps the epigastric pain or other unexplained and persistent gastrointestinal symptoms may constitute an indicator for studies on PHP in patients with FM.

The main limitation of this study was the absence of results of vitamin D dosage in our population. In PHP, the most likely cause of unusually low concentrations of vitamin D is the increased metabolic clearance induced by $1.25(OH)_2D$, and possibly by PTH, since the levels of 25(OH)D return to normal after parathyroidectomy.[19] However, the assessment of vitamin D was not performed in our comparison group, although we found significant differences in the frequency of normocalcemic hyperparathyroidism between groups.

Our study set out to be a preliminary assessment of an association between hyperparathyroidism and FM. According to our results and the few data in the literature, apparently such association exists. But longitudinal studies with larger numbers of patients and controls and with an evaluation of serum levels of vitamin D are needed to confirm whether this is only a chance association, if the increased serum PTH are part of the FM pathophysiology, or if these actually would not be cases of FM, but of asymptomatic PHP.

Hyperparathyroidism, despite having symptoms similar to FM, has different evolution and prognosis, which may progress to higher morbidity and major clinical complications that can be prevented with an early diagnosis. Although most patients with asymptomatic hyperparathyroidism present a stable disease, about 25% show evidence of progression of the disease during follow-up, indicating that it is important to monitor patients not subjected to parathyroidectomy.[24]

Thus, based on these results found, the request of a laboratory evaluation of calcium and PTH serum levels may be suggested in the evaluation of patients with FM and, in case of any change, one must continue the investigation in search of PHP. However, further studies with greater statistical power may confirm the association of the two diseases and provide better subsidies for routine assessment of the parathyroid glands in patients with FM.

Conflicts of interest

The authors declare no conflicts of interest.

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